How much evidence is provided prior to approval? An updated systematic review of biosimilar applications in Europe

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Introduction

"A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). [...] When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness."


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 September 2012
EMA/837805/2011

Questions and answers

Questions and answers on biosimilar medicines (similar biological medicinal products)

Source: Christian Schneider, Chair EMA Biosimilar Working Party: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf

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Talk last year NEW

Review of clinical development programs of
21 (+12=33) biosimilars on
7 (+4=11) different active substances approved by EMA

- Main source: European public assessment reports (EPAR)
  - Available online at http://www.ema.europa.eu
- Results:
  - High variability between submitted trials
  - High variety also within an active substance
    ➔ case by case decision of the regulators
  - Recommendation in product specific guidelines and overarching guidelines were mostly followed, but also exceptions
  - It is possible to gain approval even though not all pre-specified primary endpoints meet the target

Details can be found in: Mielke, J., Jilma, B., Koenig, F., and Jones, B. (2016) Clinical trials for authorized biosimilars in the European Union: a systematic review. Br J Clin Pharmacol, 82: 1444–1457. doi: 10.1111/bcp.13076.

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Approved biosimilars in Europe

Active substance	Originator drug name	Biosimilar
Haematopoietic growth factors		
Epoetin Alfa/Zeta	Eprex(EU), Erypo(Germany)	Silapo/Retacrit
		Epoetin Alfa Hexal/ Abseamed/Binocrit
Filgrastim	Neupogen	Zarzio/Filgrastim Hexal
		Tevagrastim/Ratiograstim/Biograstim
		Nivestim
		Grastofil/Accofil
Endocrinologically acting drugs		
Follitropin Alfa	Gonal-f	Ovaleap
		Bemfola
Insulin Glargine	Lantus	Abasaglar
		Lusduna
Somatropin	Genotropin	Omnitrope
Teriparadite	**Forteo**	**Movymia/Terrosa**

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Approved biosimilars in Europe

Active substance	Originator drug name	Biosimilar
Anti-inflammatory blockers of tumor necrosis factor alpha		
Etanercept	Enbrel	Benepali
		Erelzi
Infliximab	Remicade	Remsima/Inflectra
		Flixabi
Adalimumab	**Humira**	**Amgevita/Solymbic**
		Imraldi
Rituximab	**Mabthera**	**Blitzima**
		Rixathon/Riximyo
Anticoagulant		
Enoxaparin sodium	**Clexane**	**Inhixa/Thorinane**

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Today's focus

- How much evidence is provided?
  – guidance vs. practice
- Choice of study populations
- Pre-specification of development programs

How much evidence is provided?

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How much evidence has to be provided prior to approval?

- The required amount of information depends on the complexity of the molecule, the availability of established biomarkers and the sensitivity of clinical endpoints.
- Product-specific guidelines give advice on the set-up of the development program

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How much evidence has to be provided prior to approval?

- Example 1: Insulin glargine
- Example 2: Teriparatide
- Example 3: Enoxaparin sodium

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Insulin glargine – guidelines vs. practice

Assessment	Guideline	Practice
PK/PD	*"In addition to similar physicochemical and functional characteristics,* ***demonstration of similar pharmacokinetic (PK) and pharmacodynamic (PD) profiles is considered the mainstay of proof of similar efficacy*** *of the biosimilar and the reference insulin."*	Lusduna (Merck): 4 PK/PD studies with 285 subjects Abasaglar (Eli Lilly): 5 PK/PD studies with 231 subjects

Efficacy	*"There is* ***no anticipated need for specific efficacy studies*** *since endpoints used in such studies, usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins."*	- 2 large Phase III studies in patients with Diabetes Melltius Type I,II:
		  - Lusduna:1030 patients
		  - Abasaglar: 1295 patients
		- Extensive safety and immunogenicity assessment

Safety	*"In certain cases,* ***a pre-licensing safety study*** *including immunogenicity assessment* ***may be waived****."*	

Movymia/Terrosa (teriparatide)

- No product-specific guideline available
- Comment in the EPAR: *“small and simple biologic”*
- Conclusion of equivalence based on a 2x2 PK crossover study in healthy volunteers (54 subjects)
- No established PD marker
  ➔ initially, the sponsor did not provide any PD data
  ➔ provided additional data on PD marker (serum calcium concentration) during the application procedure
- 90% confidence intervals of the ratios of geometric means of PK parameters fell in 80-125% range, but excluded 100%

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Decision making in PK studies

"The location and the width of the confidence interval should also be taken into account in the interpretation of similarity.

For example, statistically significant differences in 90% CIs within the justified acceptance range regarding relevant PK parameters would need to be explained and justified as not to preclude biosimilarity."

18 December 2014
EMEA/CHMP/BMWP/42832/2005 Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Source: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

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  ➔ Sponsor provided justification (not clinical relevant)
- Some uncertainty concerning immunogenicity

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Movymia/Terrosa (teriparatide) - Immunogenicity

*"No analysis of immunogenicity parameters has been performed, because **the Applicant is of the opinion that a clinically relevant immunogenic potential [...] appears to be highly unlikely**, as the immunogenic potential of Forsteo has proved to be negligible in the clinical studies for registration purposes as well as over the past ten years on the market."*

*"Nevertheless the **lack of clinical characterisation of the immunogenicity [...] still presents a gap in the biosimilar exercise which needs to be addressed in an appropriate way,** especially as some differences [...] could be seen in the PK endpoints, no clinical efficacy/safety (+ immunogenicity) study was conducted or is planned and the non-clinical study does not help to dispel remaining concerns."*

➔ Sponsor offered to provide data from a Phase III study in Japan post-marketing

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Inhixa/Thorinane (Enoxaparin sodium)

- Only a PD study in 20 healthy volunteers (no PK, no efficacy, no safety)
- 80-125% equivalence margins (no justification in EPAR!)
- Sponsor planned with 90% confidence intervals (95 % required for PD endpoints), but also 95% intervals of primary endpoints were fully within the equivalence region
- Some other endpoints failed to show equivalence, sponsor claimed that this was due to higher variability on these endpoints and the powering of the study on the primary endpoint

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Guidelines on biological products containing low-molecular-weight-heparins

	First guideline (2009)	New guideline (2016)
PK	No PK studies necessary	No PK studies necessary
Route of administration	SC, in addition IV if licensed	SC only
Phase III studies	At least one efficacy and safety study Safety and immunogenicity data generated pre-marketing	No efficacy comparison necessary If justified: no safety/immunogenicity data necessary

"During the CHMP Scientific Advice (SA) procedures, the applicant claimed that PK/PD parameters [...] are more sensitive to detect potential differences in efficacy than clinical equivalence." (EPAR, 2016)

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Is the provided evidence enough?

- Approach comparable to the approach of the FDA (considers the product more as a generic than a biosimilar)
- Controversial discussion, e.g., paper by Imberti et al. (2017):
  - *"The authorizative path adopted by EMA [...] raises [...] some relevant concerns regarding efficacy and safety"*
  - *"Even stronger concerns are raised by the conclusions about safety, which are based just on a small-sized PK/PD study in healthy volunteers."*
  - *"[...] strongly advise the Italian National Health Authorities not to entrust safety assessment to the post-marketing surveillance only, but to promote well designed and powered studies aimed at establish the actual efficacy and safety [...] as already performed for other molecules"*

Imberti et al. Thrombosis Journal (2017) 15:13, DOI 10.1186/s12959-017-0136-2

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Discussion

- Some companies provide more information than (explicitly) requested in the guidelines
- Some companies seem to try to avoid unnecessary studies and to discuss intensively with regulators
- Does that depend on the size of the company?

Product	Company	Ranking by sales*	
Abasaglar	Eli Lilly	13	
Lusduna	Merck	5	
Movymia	Stada	41	Joint application
Terrosa	Gedeon Richter	64	
Inhixa	Techdow	>100	Joint application
Thorinane	Pharmathen	>100	

*Source: https://scrip.pharmamedtechbi.com/-/media/Supporting-Documents/Scrip-100/2016/Scrip100_2016.pdf?la=en

- Similar observation also in Regnstrom et al. (2010)

Regnstrom, J., Koenig, F., Aronsson, B., Reimer, T., Svendsen, K., Tsigkos, S., ... & Vamvakas, S. (2010). Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *European journal of clinical pharmacology*, *66*(1), 39.

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Study population

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Study population in PK/PD

"Healthy volunteers lack co-morbidity and co-medications and are likely to have less target-mediated clearance compared to patients. PK studies are not always possible or feasible in healthy volunteers. In this case, the PK needs to be studied in patients."

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Study population in PK/PD

Substance	Product	Volunteers?	Patients?
Rituximab	Blitzima	-	X
	Rixathin/Riximyo	-	X
Insulin glargine	Lusduna	X	X
	Abasaglar	X	X
Infliximab	Flixabi	X	-
	Remsima/Inflectra	-	X

“Due to the long half-life and immunogenicity of infliximab, a parallel group design was considered appropriate and allowed the comparison of the PK and immunogenicity of CT-P13 [Remsima/Inflectra] and Remicade in a sensitive patient population as already mentioned.”

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Study population in efficacy/safety

"The study population should generally be representative of approved therapeutic indication(s) of the reference product and be sensitive for detecting potential differences between the biosimilar and the reference."

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Study population in efficacy/safety

- In case of multiple approved biosimilars for the same active substance, the studied indication(s) is sometimes identical (3 out of 8 active substances)
- Examples for different indications studied:
  - Filgrastim: Identical study population for 3 out of 4 applications
  - Adalimumab: For Amgevita/Solymbic additional study in Psoriasis (in addition to Rheumatoid arthritis (RA) patients)
  - Etanercept:
    - Benepali: RA
    - Erelzi: Plaque psoriasis

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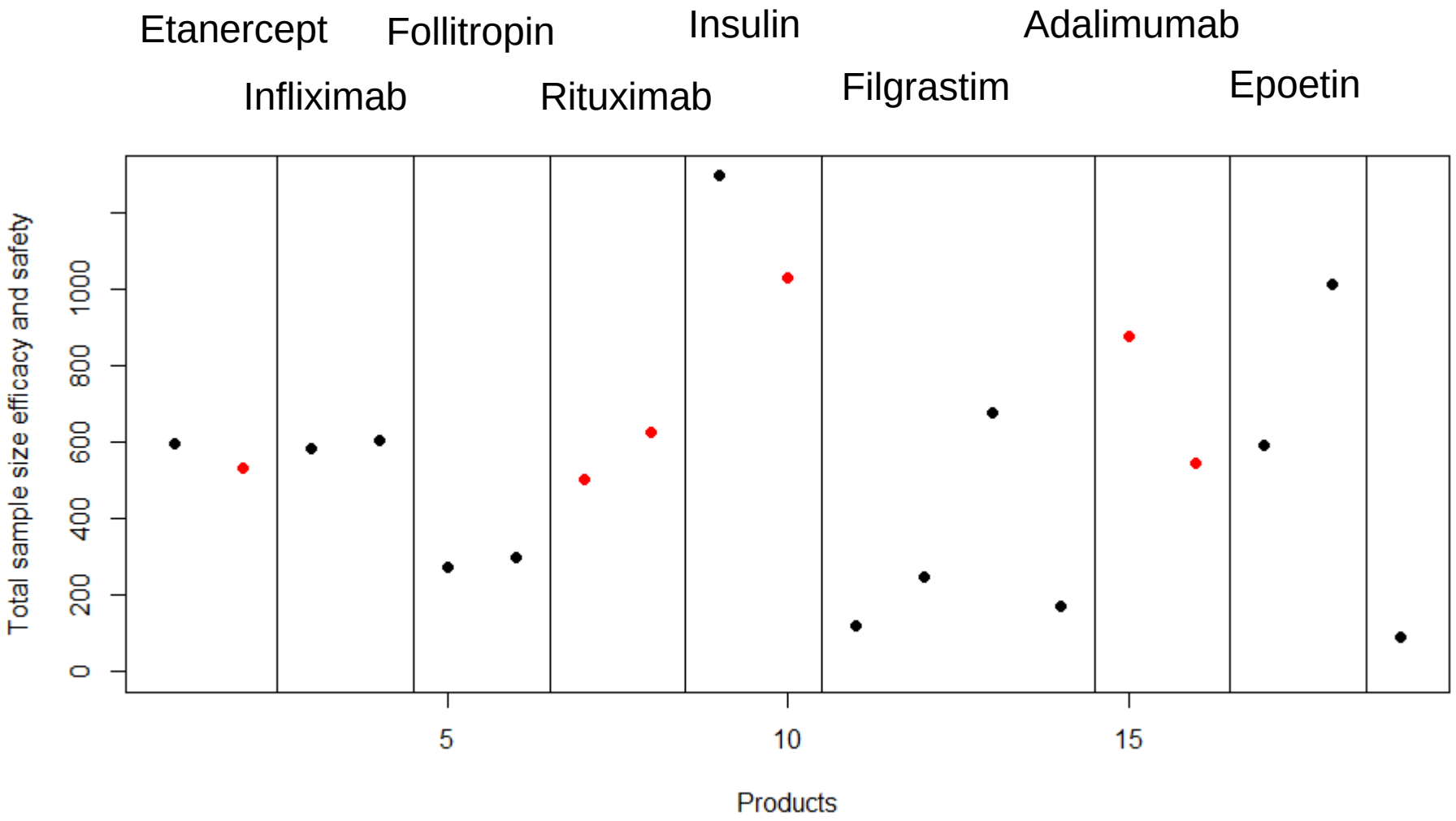
Sample sizes for efficacy & safety



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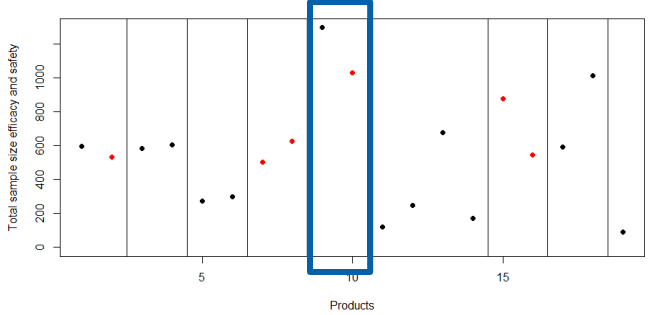
Insulin glargine



	Lusduna	Abasaglar
Type I Diabetes Mellitus	502	536
Type II Diabetes Mellitus	528	759

- Very similar set-up of the studies (treatment duration, endpoints, margins)
- Sample size calculation:
  - Abasaglar: study was powered for 99% (!) power to show non-inferiority
  - Lusduna: no information on sample size calculations in EPAR

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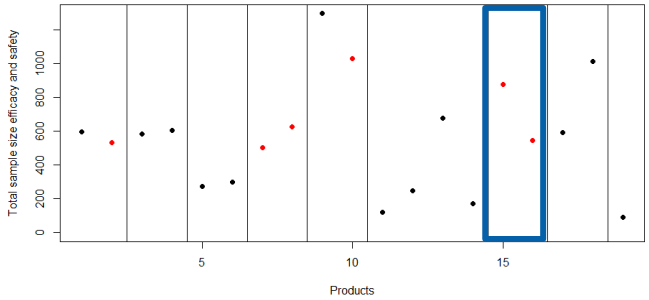
Adalimumab



- 2 applications
  - Amgevita/Solymbic
  - Imraldi
- PK/PD development programs comparable
- Both presented one study in RA with comparable sample sizes
- For Amgevita/Solymbic: additional study in psoriasis with 350 subjects
- Unclear from the EPARs why additional study was conducted

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Discussion

- Study populations not necessarily the same between different applications
- Sample size calculation in Phase III mostly consistent (if same indication, endpoint and margin ➔ comparable sample size)
- Some differences in sample size can be explained by realizing that some sponsors conducted additional studies (e.g., other populations)
- Reasons for additional studies not included in EPARs

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Pre-specification of development programs

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Overview

- In general, margins, endpoints and analysis are to be pre-defined
- In practice there seems to be some flexibility
  - Multiple PK/PD studies, not all studies/endpoints are successful ➔ approval*
  - Study failed ➔ sponsor was encouraged to repeat the study
  - Margins were chosen too wide ➔ after seeing the results, the decision was made that the analysis is nonetheless acceptable

* Details:

Mielke, J., Jilma, B., Koenig, F., and Jones, B. (2016) Clinical trials for authorized biosimilars in the European Union: a systematic review. Br J Clin Pharmacol, 82: 1444–1457. DOI: 10.1111/bcp.13076 .

Mielke, J., Jones, B., Jilma, B., Koenig, F. (2017) Sample size for multiple hypothesis testing in biosimilar development. Statistics in Biopharmaceutical Research. DOI: 10.1080/19466315.2017.1371071

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Choice of margins

- Margins are to be pre-specified and statistically and clinically justified
- Justification for Phase III seems to be mostly provided (but not always stated in EPARs)
- For PK/PD, mostly the standard 80-125% equivalence margins from bioequivalence are used, sometimes pre-defined
- Can be discussed in scientific advice, but not mandatory

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Consequences if chosen margins appear too wide

- Amgevita/Solymbic:
  - Phase III study in RA patients (larger of two studies)
  - *"The choice of the 0.738 margin on a multiplicative scale would correspond to an absolute margin of more than -16% on the additive scale.* ***This could be considered too wide. However, in light of the results observed this does not represent an issue that could compromise the reliability of the study."*** *(EPAR)*
- Zarzio/Filgrastim Hexal
  - PK/PD study (single-arm Phase III)
  - "*It was assumed that the smallest clinically relevant difference in PD response between the test and reference product was 15% of the effect observed for Neupogen compared to placebo in the published study.* ***Decreasing this margin to 10% [...] would result in more acceptable equivalence intervals; indeed, the 95% CI [...] would still fall within these tighter equivalence boundaries."*** *(EPAR)*

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Discussion

- If pre-specified margins are used, an equivalence testing approach has known operating characteristics and a controlled Type I error rate (“consumer’s risk”)
- Posthoc changes of the margin won’t control Type I error rate
  - E.g., if the margin is considered to be too wide (not informative) and the conclusion is made based on the observed confidence interval, this is not a well-defined formal testing procedure anymore

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Conclusions

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Conclusion

- Regulatory standards still evolving
- Still differences between biosimilar development programs (also within same active substance)
- Many non-standard approaches
  - Stopping at interim in PK, switching designs, applications without Phase III, ...
- Alternative routes possible other than proposed in guidelines
  - Application for Inhixa/Thoranine used an alternative approach to the one in the guidelines
- Sometimes lack of information on important features in EPAR
  - Justification/Pre-specification of margins, trial design & strategy, ...

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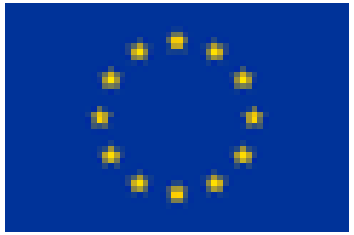
Thank you



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